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Review

Therapeutic failure of primaquine and need for new medicines in radical cure of *Plasmodium vivax*

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ABSTRACT

Primaquine has been the drug of choice for the prevention of *Plasmodium vivax* relapse for more than 60 years. Primaquine tolerant strain of *P. vivax* was identified in 1944. Significant mortality and disease burden of *P. vivax* calls for the need of new drugs. Primaquine resistance is a complex issue, as the mechanism of resistance is not clear. Direct evidence of resistance to primaquine by hypnozoites has not yet been shown. There are some reports detailing risk of primaquine resistance in specific regions, but the overall distribution of primaquine resistance in *P. vivax*-infected people is largely unknown. Confounding factors contribute to treatment failures; such as inadequate doses, inappropriate dosing intervals, risk of reinfection, combinations with blood schizontocidals, and compliance. Therefore, primaquine resistance needs to be addressed along with additional important confounding factors. Tafenoquine is the most studied drug in replacing primaquine for the radical cure of *P. vivax* malaria. It has comparable efficacy with primaquine. The potential advantage of tafenoquine is better compliance with a single dose regimen. Rational use of primaquine can secure its effectiveness, but it is essential in the future to have better or similar alternatives to treat *P. vivax*.

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1. Introduction

Primaquine is the drug of choice for the treatment of *Plasmodium vivax* (Krudsood et al., 2008). It is recommended by World Health Organization (WHO) and approved by the United States Food and Drug Administration (FDA) for prevention of *P. vivax* malaria relapse (Fernando et al., 2011). In most of the countries for many years, it has been the only drug used to cure *P. vivax* infections (Krudsood et al., 2008). In this review, we discuss the potential treatment failure or suspected resistance by hypnozoites to primaquine reported and the need for discovering new drugs as replacement for primaquine.

Malaria is one of the re-emerging infectious diseases worldwide (Nchinda, 1998). *P. vivax* is one of the malaria-causing parasites. (CDC, 2013a) Traditionally, P. vivax caused malaria was considered as a mild form of malaria, but that concept changed widely. *P. vivax* caused malaria is a pernicious infection often associated with complications leading to death (severe anemia, severe thrombocytopenia, respiratory distress, renal or hepatic failure, coma, and shock) (Baird, 2013). The reported rate of relapse vary from 0 to 100%. The rate of relapse in one study is more than 1 person out of 5 (Baird and Hoffman, 2004), but in those who are infected with the Chesson strain 80% of relapses occurred within 30 days of initial treatment with quinine. Chesson strain isolated from New Guinea in 1944 was found to be tolerant to primaquine. The strain was

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named after the patient from whom it was obtained. It is surprising to see that there were no serious efforts for long time; to develop better drugs to manage such strains (White, 2011).

After the parasite enters the blood via the Anopheles mosquito, it travels to the liver and makes merozoites. These merozoites invade red blood cells and destroy them. After 48–72 h, the common signs and symptoms of disease such as fever and weakness are manifested. The parasite causes a weak provocation of the human immune system; therefore, re-infection can easily occur after a while in susceptible individuals. Re-infection and relapse in the patients who are infected with *P. vivax* need to be further studied for their mortality and disease burden (CDC, 2013a).

The relapse is happening because of the activation of quiescent liver-stage developmental forms of *P. vivax*, termed as hypnozoites. While the patient is initially treated with quinidine or chloroquine, these dormant forms remain in an inactive state. After weeks to months, the hypnozoites become activated and relapse may occur (Bledsoe et al., 2009). If relapse is to occur with *P. vivax,* this usually happens within 6 months of the initial treatment (Baird and Hoffman, 2004). From couple of studies, it was observed that in most cases the genotype of the parasite isolates in relapse is different from that of the parasites that caused the primary infections (Collins, 2007).

Out of the 5 '8-aminoquinolines' which have ever been used to treat *P. vivax*, only two are still available: primaquine and tafenoquine. Primaquine was discovered in 1940s. It gradually became the drug of choice in prevention of *P. vivax* relapse because of its high efficacy and safety compared with pamaquine (the first drug to treat *P. vivax* malaria relapse). Quinocide and bulaquine were earlier used in the former Soviet Union and India, respectively. All '8-aminoquinolines' are believed to work though highly reactive oxidant metabolites. The exact mechanism of how primaquine eliminates hypnozoites from liver remains unclear (Petersen et al., 2011; Recht et al., 2014) (Table 1).

2. Primaquine resistance concerns

Rational use and preventing resistance are the key issues with primaquine use. Primaquine has been used for more than 60 years with anticipated high effectiveness in curing *P. vivax* infection. Its effectiveness has always been challenged with availability, prescribing practices, and adherence. Unfortunately G6PD deficiency and *P. vivax* generally affect same population more often. Fear of hemolytic toxicity significantly decreases effectiveness of primaquine (Howes et al., 2013).

According to WHO, antimalarial drug resistance is happening due to spontaneous mutation. The exact mechanism of resistance is clearly described for chloroquine, while for primaquine and other 8-aminoquninolone compounds, it has not been identified (Buchachart et al., 2001). Primaquine resistance is commonly confused as failure of therapy or inability to remove the hypnozoite liver stage of *P. vivax* after the full course of therapy and correct therapeutic dose (Recht et al., 2014). Subsequently, confirming true primaquine resistance is controversial.

The chance for increased resistance relates to the correct dose and duration of therapy of primaquine. According to many studies, the proper dose and duration of therapy is a key in decreasing the risk of relapse (Buchachart et al., 2001). In a review by Baird and Hoffman (2004), reported cases of primaquine resistance over 30 years indicated that a large number primaquine therapy failure was seen with patients taking 15 mg/day for 5 days. The standard adult dose and popular dose of primaquine is 15 mg/day for 14 days (210 mg total). However, studies from several countries have shown that this dose is no longer effective (Baird and Hoffman, 2004; Buchachart et al., 2001). Higher doses of primaquine might be needed for complete eradication of the parasite. A single 45-mg dose administered once per week for 8 weeks (360 mg total) has been proven to be as effective (usually 100%) as 30 mg daily for 14 days (420 mg total) or 60 mg daily for 7 days (420 mg total) (Baird and Hoffman, 2004; Buchachart et al., 2001). An Australian study confirms the significantly high effectiveness of high-dose primaquine therapy in preventing relapse (Townell et al., 2012).

In addition to using the proper dose, another trial has demonstrated that even a high dose of primaquine without a schizontocidal agent, raises the risk of relapse to more than 80% (Fernando et al., 2011). Primaquine is usually combined with an appropriate blood-stage antimalarial agent, such as quinine or chloroquine. These drugs remove parasites in the asexual blood stage and neutralize the infectivity of mature *P. vivax* gametocytes. Therefore, they reduce the risk of resistance by affecting the blood stage of malaria (Townell et al., 2012). High dose primaquine therapy with a schizonticidal agent is the preferred to decrease chances of relapse.

Although if someone relapses after taking these agents properly; connecting the failure of therapy to a specific agent is difficult. In addition, people who take medication for the prevention of relapse and then travel to regions with a high risk of reported malaria prevalence may get re-infected. In this case, it should not be considered as relapse and resistance (Baird, 2009; Price et al., 2007).

The other important factor in detection of therapy failure with primaquine is adherence to medication. A study was conducted to examine the effect of compliance to full course of primaquine on the rate of relapse in *P. vivax*-infected individuals. The patients were assigned into 2 groups. Both received primaquine 15 mg once daily for 14 days after taking chloroquine (total of 2.5 g over 3 days). Administration of therapy for one group was directly observed, and the other group self-administered primaquine. The results showed that 5 out of 46 patients in the self-administered group experienced relapse, while the patients in the direct observation group had no cases of relapse. This information indicates the importance and effect of compliance with primaquine on the rate of relapse with *P. vivax* malaria (Takeuchi et al., 2010). However, this information alone is not enough to differentiate between treatment failure and resistance.

3. Reports on suspected primaquine resistance

In confirming resistance to primaquine, many factors are involved and should be clarified. The resistance to primaquine has already been detected in various geographical areas. The main challenge is to differentiate between reinfection and relapse. Some of the studies clearly differentiate between reinfection and relapse and who primaquine is effective in preventing relapse (Sutanto et al., 2013; Nelwan et al., 2015; John et al., 2012).

The clinical data obtained from treatment of 60 soldiers who had infections of *P. vivax* malaria since returning from Somalia and treated with 15 mg/day primaquine for 14 days indicated that 26 out of 60 soldiers experienced relapse; 8 soldiers had a second relapse (Smoak et al., 1997). There was no mention of any problems with compliance, but in a crisis situation medication adherence is expected to be less. The dose of primaquine was also low. Evidence on primaquine resistance is unclear from this study.

In a case report of a 21-year-old male US Army Ranger deployed to Afghanistan and Iraq from March to May 2003, a diagnosis of *P. vivax* malaria was made upon his return. Initially, he received quinine and doxycycline, which excluded a chloroquine-resistance infection. Primaquine was added at twice the standard dose. After 5 months, the patient reported a relapse in absence of re-exposure and strict adherence to primaquine. He was treated with chloro-